## REMARKS

Claims 1, 35-36, 42-45, and 47-51 will be pending upon entry of the amendment shown above. Claims 2-34 were canceled previously. Claims 37-41 and 46 are canceled by the present amendment and new claims 47-51 are added. Claims 1 and 45 have been amended to delete the phrase, "binds an IL-15R but fails to fully activate signal transduction through the IL-15R," and to specify that the mutant IL-15 polypeptide has a substitution of aspartate for glutamine at positions 149 and 156 of SEQ ID NO:4 (the wild type IL-15 sequence, having Gln/Q at positions 149 and 156). Support for this amendment is found, for example, in original claim 8. Claims 1 and 45 have also been amended to delete the phase "being optionally." Claim 43 has been amended to replace "90%" with "95%." Support for this amendment is found, for example, at page 13, line 12. New claims 47-51 are similar to pending claims 35, 36, 42, 43, and 44, respectively, except that new claims 47-51 depend from claim 45 rather than from claim 1. No new matter has been added.

The present amendments are made solely to facilitate the finding of allowable subject matter. Applicants expressly retain their right to pursue previously disclosed and/or claimed subject matter without prejudice or disclaimer.

35 U.S.C. § 112, ¶ 1

*Enablement*

In the Office action mailed February 2, 2007 ("the Office action"), claims 1, 35-36, and 42-46 were rejected as failing to comply with the enablement requirement (Office action at pages 2-6). The Examiner found that the specification *was* "enabling for a composition comprising a mutant of IL-15, said mutant having mutations at positions 149 and 156 of the wild type IL-15, wherein glutamine is replaced with an aspartic acid, fused to the Fc region of immunoglobulin, or a composition comprising IL-2 fused to the Fc region of immunoglobulin" (Office action at page 2). "However, the specification fails to disclose a therapeutic composition which comprises ... 'all possible' mutant IL-15 polypeptides" (Office action at page 3).

In view of the present amendment, the Examiner is asked to reconsider and withdraw this ground for rejection. Both of Applicants' independent claims (claims 1 and 45) now require a mutant IL-15 polypeptide that includes a substitution of aspartate for glutamine at positions 149

and 156 of SEQ ID NO:4. As Applicants made IL-15 mutants having the very mutations now recited in the claims and demonstrated their ability to target the IL-15R, it is their position that the subject matter now claimed was enabled by the specification (*see, e.g.*, page 38, lines 13-17, where Applicants teach that their double mutant IL-15 polypeptide inhibits cellular proliferation, and in a dose-dependent manner according to the two dosages tested, and page 46, lines 5-8, where Applicants teach that the IL-15 mutant fused to Fc "markedly reduced the proliferation frequency of CFSE-labeled T cells"). In addition to the working examples provided with respect to the mutant IL-15 polypeptide, and as the Examiner has acknowledged, the level of skill in the art is high and neither the IL-15 polypeptide nor methods of introducing mutations into a polypeptide are new. Thus, at least these factors weigh in favor of enablement. Given the present amendment, which should address many of the Examiner's concerns regarding the use of "all possible" IL-15 mutants, the rejection for lack of enablement should now be withdrawn.

*Written Description*

Claims 1, 35-36, and 42-46 were rejected as allegedly failing to comply with the written description requirement (Office action at pages 6-7). The Office action states that "the disclosure of one mutant does not provide written description for 'all' possible IL-15 mutants that retain the desired activity, nor does it provide written description to [a] IL-15 mutant polypeptide that is at least 90% identical to wild-type IL-15 which also retains specific desired activities" (page 7).

Although the Office action provides no specific basis for this assertion, Applicants note that the amended claims recite subject matter amply supported by structural limitations (*i.e.*, mutant IL-15 polypeptide with two specific mutations). The structural limitations have a demonstrated correlation with function (*i.e.*, inhibition of IL-15 signaling). Thus, the rejection based on lack of support for "all possible" IL-15 mutants cannot be sustained. Withdrawal of the rejection of claims 1, 35-36, and 42-45 is respectfully requested.

*New Matter*

Claims 1 and 45 were rejected as allegedly containing new matter for containing the phrase, "binds an IL-15R but fails to fully activate signal transduction through the IL-15R." Although Applicants disagree that this phrase adds new matter (see the specification at page 12, lines 8-9), this rejection is met by the deletion of this phrase.

35 U.S.C. § 112, ¶ 2

Claims 1 and 45 were rejected as indefinite for reciting the phrase, "...but fails to fully activate signal transduction through the IL-15R". This rejection is met by the amendment to claims 1 and 45 to delete this phrase.

Claim 44 was rejected for reciting the phrase, "is a target cell depleting Fc region." The Office action stated that "it is unclear what is a target-cell deleting [sic] FC regions" (page 8).

Applicants respectfully traverse this rejection. The terms of the claims are interpreted in view of the specification and, here, Applicants teach (specification at page 14, lines 27-29):

> The Fc region may ... be target-cell depleting (*i.e.*, able to destroy cells by binding complement or by another mechanism, such as antibody-dependent complement lysis.

In addition, the structures of target-cell depleting Fc regions (as well as non-target-cell depleting Fc regions) are described in detail in the specification at page 15, line 27, to page 16, line 14. In view of the definition and structural details provided in the specification, the meaning of "target-cell depleting Fc region" is clear. Withdrawal of this rejection is respectfully requested.

35 U.S.C. § 103

Claims 1 and 35-46 were rejected as unpatentable over Kim *et al.* (*J. Immunol.*, 160:5742-5748, 1998, "Kim") in view of Strom *et al.* (*Transplant. Proc.*, 27(5):18-20, 1995; "Strom"). According to the Office action,

> [t]here would have been a great expectation of success that [combining] the IL-15 mutant/Fcγ2a taught by Kim et al. and the IL-2Fcγ2a chimera taught by Strom et al. would result in a therapeutic agent, because each is taught in the prior art to be useful for the same purpose, i.e, as an immunosuppressive agent, *In re Kerkhoven, 626 F.2d 846, 850, 205 USPQ 1069, 1072 (CCPA 1980).* One of ordinary skill in the art would have been motivated to combine the teachings of Kim et al. and Strom et al., because each reference teaches an agent for the treatment of autoimmune diseases or organ transplantation, and it flows logically that the combined composition would be expected to be useful in the treatments of said diseases.

Applicants respectfully traverse. The fact that two therapeutic agents were reported to have immunosuppressive activity is no indication that they would necessarily work together, or

that they would work better than each agent alone. IL-2 and IL-15 have overlapping activities because they bind to the same β and γ receptors (Kim, page 5746, carryover sentence from left column to right column). It does not flow logically that a combination of agents having an overlapping receptor specificity would be useful. To the contrary, one is more likely to expect that such agents have redundant functions. The Examiner's attention is kindly directed to the specification at page 2, line 27, where Applicants refer to "the conventional wisdom that IL-2 and IL-15 are redundant". Similarly, Kim used knowledge of IL-2 to move from an IL-2-related treatment to an IL-15-related treatment, but never suggested that the two agents should be combined. Kim states that since "in vivo administration of an IL-2 diphtheria toxin-related fusion protein blocks DTH...we postulated that IL-15R targeted treatment, as previously documented for IL-2R-targeted treatment, *would also* inhibit Th1-dependent in vivo responses" (Kim, page 5747, left column, second full paragraph). This indicates that an IL-15R targeting agent is interchangeable with an IL-2R targeting agent. There is no motivation to use two such agents together.

Applicants disagree that *In re Kerkhoven* is relevant to considerations of obviousness in this case. *In re Kerkhoven* concerned claims to combinations of detergents. Prior art describing the properties of various detergents may be suggestive, where it is common to mix them based on shared properties. This principle is not applicable to all technical fields. There is no indication in the cited art that it is common to create mixtures of therapeutic polypeptides simply because they share a biological function.

The claimed compositions arise from the inventors' discovery of novel ways to inhibit the immune response. The combinations provide an agent which promotes activation induced cell death (IL-2/Fc), and an agent which antagonizes IL-15 and thereby promotes passive cell death (mutant IL-15) (specification, page 10, lines 24-29). The ability of IL-2/Fc to promote activation induced cell death is not suggested or recognized in the cited references, not to mention its use in combination with an agent that promotes passive cell death.

In addition, the inventors have discovered that the claimed combinations have unexpected potency. The specification describes an experiment in which mice received transplants of allogeneic skin grafts. Administration of a composition including both mutant IL-15/Fc and

IL-2/Fc more than doubled the mean survival time of functioning grafts as compared to graft survival in animals administered a composition including only one of the agents (specification, page 48, lines 12-22, and Figure 12). Thus, a combination of agents having these features provides superior immunosuppressive effects.

In conclusion, Applicants respectfully submit that the cited references fail to suggest the claimed therapeutic compositions, and respectfully request withdrawal of this rejection.

## CONCLUDING REMARKS

*Initialed IDS*: In the Office action mailed April 19, 2006, the Examiner stated that the information disclosure statements submitted on December 12, 2003, August 23, 2004, and January 30, 2006, had been considered. The U.S. patents, foreign patents, and published patent applications (listed on sheet 1 of four) on the Forms-1449 submitted with the information disclosure statement of December 12, 2003, were not initialed. In the Amendment filed October 19, 2006, Applicants respectfully requested initialed copies. Applicants again respectfully request that the Examiner provide an initialed copy. A copy of the partially initialed form is attached.

A Petition for Extension of Time, Request for Continued Examination, and required fees are being filed herewith. Please apply any other charges or credits to deposit account 06-1050, referencing attorney docket no. 13985-057002.

Respectfully submitted,

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